# Cell Cycle

## Introduction

This lesson will be a hefty review of physiology. We will discuss the phases of the cell cycle—just what they are and what happens. We will also use this as an opportunity to review the steps of mitosis, getting into the details of the microtubule interaction to form the spindle. The phases of the cell cycle will be used to address cell cycle checkpoints and regulation (#6 *Cell Cycle Regulation*) and the escape into malignancy (#7 *Biology of Cancer*), and the emphasis on microtubules will build on information learned in General Physiology to understand how chemotherapy works (#8 *Cycle and Chemotherapy*). This may feel like an MCAT review. That's okay—without it, the later material will be pretty challenging.

## Cell Cycle Overview

The cell cycle can be divided into **interphase** (not mitosis) and **mitosis** (yes mitosis). Interphase is any stage of the cell cycle, including $G_0$, that is not mitosis.

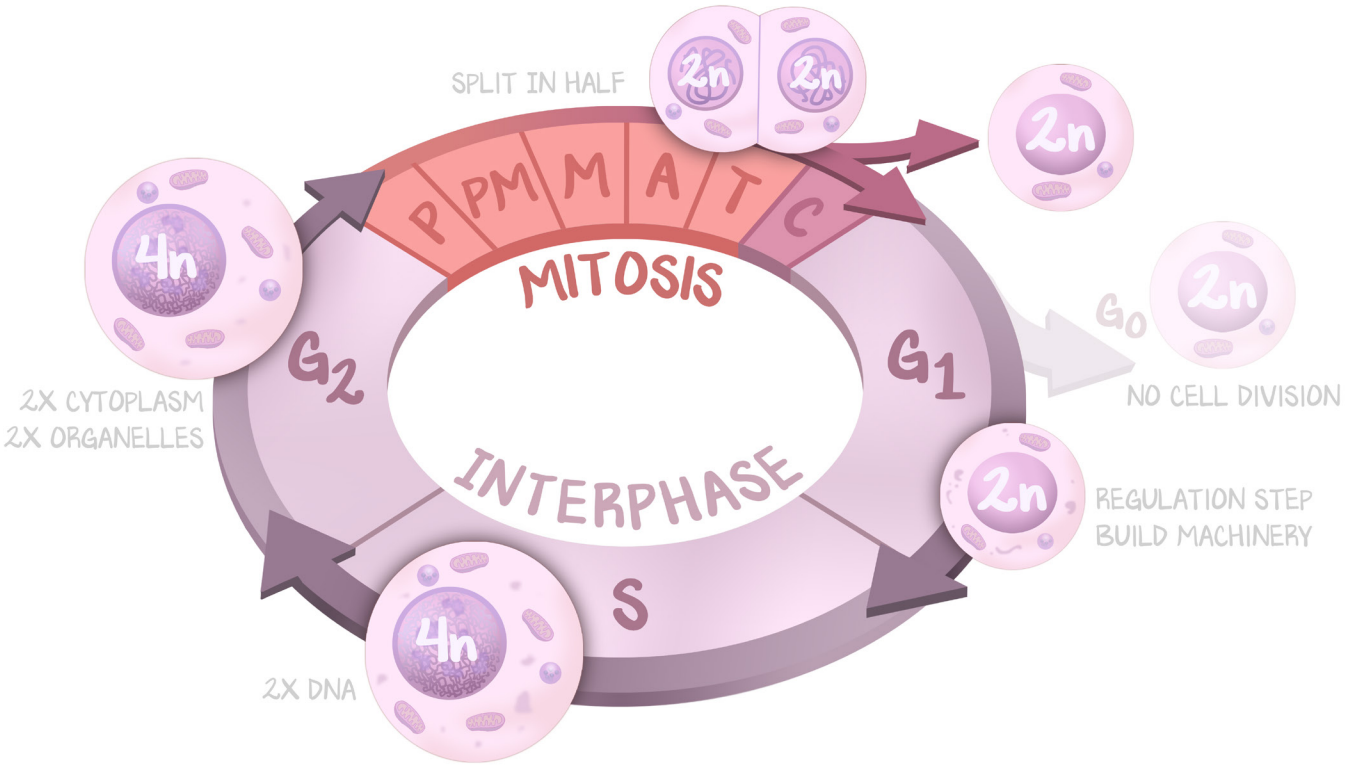


**Figure 5.1: Cell Cycle**
Pictographic representation of the cell cycle, demonstrating that it is unidirectional, moving through $G_1$, S (where nuclear content is doubled), $G_2$, and into mitosis. The phases of mitosis are discussed later.

The cell cycle is a **continuous**, **unidirectional** cycle. It always goes in the same order. The durations of the S, $G_2$ and M phases are fixed. The cell cycle duration, therefore, is influenced by whether or not a cell enters $G_0$—the resting phase—and how often it reenters $G_1$.

**$G_0$** is the phase of exit. When a cell has differentiated and no longer receives a signal to proliferate, that cell is shifted to the $G_0$ phase. In this phase the genes of that cell's activity are expressed, and that cell does whatever it does. Cardiac myocytes contract, β-islets of the pancreas secrete insulin, and neurons

fire. All of the DNA, all of the cellular machinery is focused on making the proteins that let that cell perform its designated task. Cells that can leave $G_0$ and return to the cell cycle are stable cells. Those that cannot leave $G_0$ are permanent cells. Those that rarely enter $G_0$ are called labile cells (more on this in the next section).

**$G_1$** is the first growth phase after mitosis. The cell has a complete complement of DNA, 2n genes, a total of 46 chromosomes. A cell in $G_1$ may express some of the proteins that let it do what it does, as in the $G_0$ phase. But $G_1$ should be seen as **preparation for S phase**. $G_1$ isn't actually a "growth" phase, per se, as nothing grows. $G_1$ is where the cell decides whether it's allowed to proliferate or not. In addition to the cell's functional genes, the other genes that are activated during $G_1$ are cell cycle regulation genes. The closer it gets to being allowed into S phase, the more genes of replication are expressed, making the proteins and cellular machinery required for **replication**.

**Synthesis** (S phase) is where the DNA is replicated. Each chromosome is duplicated in segments called **replicons**, which are then ligated together. Every chromosome is replicated once and only once. Every chromosome is replicated in its entirety. At the end of synthesis, the nuclear material doubles, represented as 46 chromosomes, each with two sister chromatids, with a genetic complement that represents 4 copies of each gene, for a total of 92 chromatids.

**$G_2$** is the second growth phase. It's where the cell **doubles in size** (cytoplasm, organelles) as it prepares to become two identical cells. $G_2$ ends with mitosis, where the chromatids are pulled apart from each other, resulting in two identical cells with 46 chromosomes, 2 copies of each gene. Some checks are made to the DNA in $G_2$ to make sure everything looks good. But $G_2$ is mainly about making the cell big enough to be cut in half, leaving enough cytoplasm and organelles for both daughter cells to live. This still has 4n genetic material, 46 chromosomes, 92 chromatids.

**Mitosis** (M phase) is the actual cell division. Two daughter cells are made from the one parent cell. The duplicated DNA is separated exactly equally into the daughter cells—DNA must be exactly conserved. The extra cytoplasm and organelles that were grown during the $G_2$ phase are also divided into the two daughter cells. Unlike DNA imbalances, small differences in cytoplasm and organelles are well tolerated. The 5 steps and 1 event of mitosis are discussed below. Mitosis begins with 4n genetic material and results in two cells, each with 2n genetic material.

## Cell Types

**Labile cells** are often inside the cell cycle. Tissue that requires constant cellular production, or epithelial lining that requires turnover, are labile cells. **Bone marrow**, **skin**, **hair**, and **GI epithelium** all represent the rapidly growing (that is, rapidly dividing) tissue. Labile cells are those **most vulnerable to chemotherapy**, as most chemotherapeutic agents attack cells in the cell cycle. Which is why patients on chemotherapy often complain of hair loss, gastrointestinal upset, and pancytopenia. Labile cells inherently have constant cell turnover—they "never" go into $G_0$. Each cell division is an opportunity for DNA replication errors, for recombination, and therefore for malignant transformation. **Skin cancer** is by far the most common cancer in humans; the skin has constant turnover and regular exposure to carcinogenic UV light.

**Stable cells** can go into the cell cycle, but must be **induced** to do so, usually for healing after an injury. This is most parenchymal cells of most organs, famously demonstrated by the regenerative power of the liver. It's best not to attempt to remember the stable cells. Labile cells are those listed, permanent cells should be committed to memory, and then stable cells represent the rest of cells.

**Permanent cells never re-enter the cell cycle**. They have both differentiated and exited the cell cycle. **Brain, cardiac muscle,** and **skeletal muscle** represent the classic permanent cells. This is why a myocardial infarction or stroke are so important—once damaged, there is no getting it back. If these cells are killed, they are replaced only with scar. But there is a benefit to cells outside the cell cycle. Just as labile cells were most vulnerable to chemotherapy side effects, permanent cells escape side effects from those chemotherapeutic agents that target the cell cycle (there are definitely cardiotoxic chemotherapeutics, so be careful about generalizing). And, as the reverse of labile cells, malignancy of these tissues is substantially less common than cancers of labile cells, and often represents an inherited, rather than acquired, genetic dysfunction.

## Phases of Mitosis

The five phases of mitosis (prophase, prometaphase, metaphase, anaphase, telophase) are continuous but five distinct phases helps keep track of what those continuous processes are. Mitosis ends with an event called cytokinesis. The **major difference between mitosis and meiosis is that there is no lining up of sister homologous chromosomes** in mitosis; all 46 line up to be separated as chromatids.

**Prophase** starts with the **condensation** of DNA into chromosomes, dissolution of the nuclear membrane, and the formation of **centrosomes**. Two **centrioles** make up each centrosome (along with some other less important proteins). The centrosomes start in the cytoplasm and migrate apart from each other, already possessing an early spindle. The nuclear envelope starts to break down and the DNA begins to condense, but does not yet have that karyotype-pattern butterfly condensation. **Laminin** is responsible for the nuclear membrane's dissolving while **histone 1** (H1) allows euchromatin to condense into chromosomes.

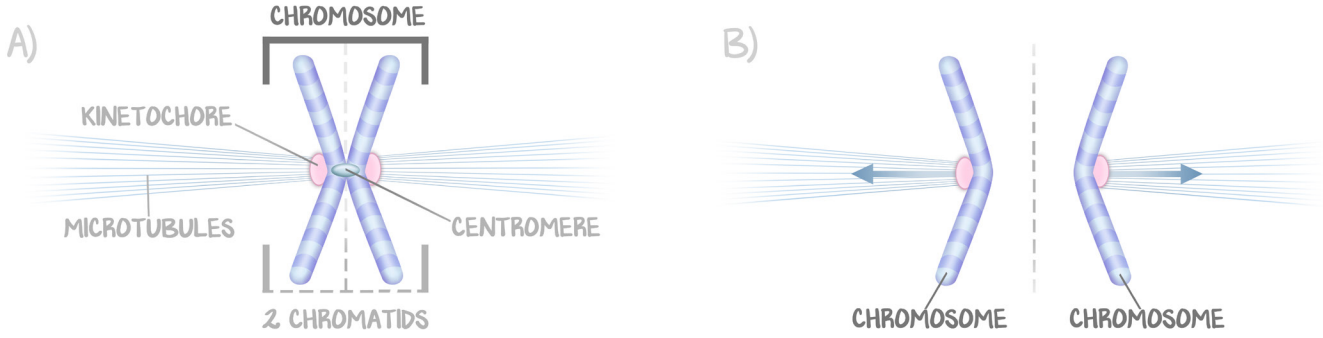


**Figure 5.2: Centromere Vocabulary**
(a) Getting the vocabulary straight is important. A chromosome is a consecutive DNA piece. The metaphase chromosome, while it has two copies of everything (it has two chromatids), those two chromatids are connected by a common link of DNA. Because they are continuous with each other, it's considered to be a chromosome. The centromere is the region where they are linked. The kinetochore is the specific machinery at the centrosome where the microtubule spindles interact. (b) After separation, the two chromatids are then referred to as chromosomes.

**Prometaphase** is between prophase and metaphase. The **chromosomes** are condensed and the **sister chromatids** connected by their **centromere** can be clearly seen. The **centrosomes** have migrated to the edges of the cell. Where the two centrosomes anchor to the cell membrane are called **poles**. The mature microtubule **spindle** originates from each centrosome and sends microtubule connections to the centromeres of chromosomes. The chromosomes are not quite lined up at the metaphase plate, but are on their way. There is a give and take of microtubules as the two poles elongate or shorten their microtubules to align the chromosomes. The nuclear envelope is almost gone, but not quite.

**Metaphase** shows complete dissolution of the nuclear membrane and the chromosomes lined up at the **metaphase plate** (the middle of the cell, equidistant from the two poles). **Microtubules** from **centrioles** have **inserted** at the **centromere** of the sister chromatids, attached specifically to the **kinetochore**. The centromere is the region where the two chromatids are linked; the kinetochore is the protein apparatus at the centromere that microtubules attach to. Centrosomes are the things at the edge of the cell, and they are made of centrioles. The cell is ready to pull the chromatids apart from one another.

**Anaphase** begins as the chromatids separate and the microtubules shorten towards the centrioles. Sister chromatids separate from their centromere, and now, as chromosomes, are pulled apart towards the centrosomes, towards the poles. There is random variation of the placement of cytoplasm and organelles, but the two cells will be about even. Anaphase ends as the nuclear envelope begins to develop around the chromosomes closely tethered to the cell poles.

**Telophase** is the reconstitution of the genetic material back into unwound DNA, the formation of the nuclear pore, and the dissolution of the centrosomes. The microtubule spindle breaks down. The cell membrane between the two daughter cells invaginates under the influence of actin filaments.

Mitosis ends with **cytokinesis**, the process in which the two cells finally separate.

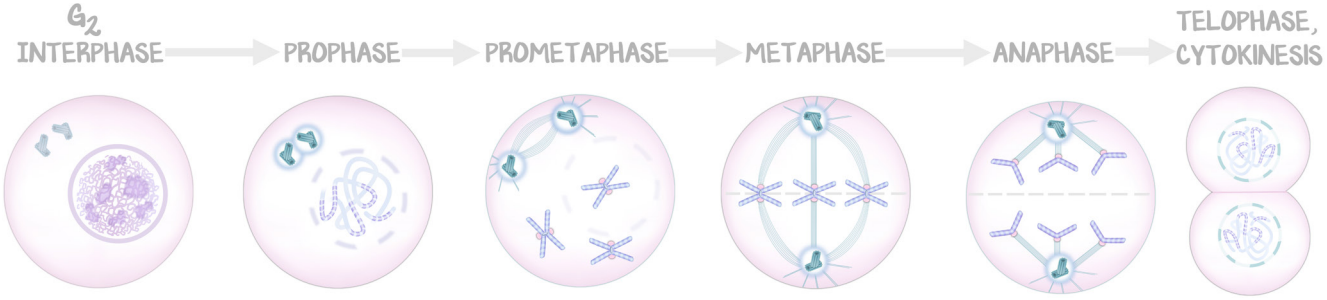


**Figure 5.3: Stages of Mitosis**
$G_2$ of interphase shows nearly a doubly sized cell, with nuclear material as expected in interphase, a mix of heterochromatin and euchromatin. Prophase shows early condensation of DNA, the initial loss of the nuclear envelope, and formation of the mitotic spindle. Prometaphase has those butterfly-shaped chromosomes but without alignment at the metaphase plate; the spindle has formed. Metaphase shows the alignment of the chromosomes and the maturation of the spindle. Anaphase demonstrates individual chromatids, now called chromosomes, being pulled, in line with each other, away from the metaphase plate towards the poles. Telophase is the uncondensing of the nuclear material and reformation of the nuclear envelope, and ends with cytokinesis.

## Microtubules

The cytoskeleton microtubules are harvested from interphase to create the spindle. Cytoskeleton microtubules must be disassembled from interphase, then reassembled as mitosis microtubules. When mitosis is over, the spindle is disassembled and microtubules are built back into cytoskeleton. Cytoskeleton microtubules are discussed in detail in General Physiology Lesson #4 *Cytoskeleton*. This is one reason why a cell set in motion along the cell cycle must dedicate its energy and focus on mitosis; the microtubules usually used to shuttle around vesicles are now required for mitosis.

Microtubules in mitosis are organized by centrosomes. A **centrosome** is a complex of proteins; the important players are the **centrioles**. The centrioles are a microtubule-organizing apparatus, similar to the basal body of a flagellum. Centrioles are each made of **nine microtubule triplets**. From the centrioles the spindle is formed. Centrioles are oriented at ninety degrees to each other, projecting astral microtubules to the cell membrane (the anchor) and kinetochore microtubules to the kinetochore of chromatids.

**Astral microtubules** are those microtubules connected from the centrosome to the cell membrane, the anchoring microtubules that allow the centromere to offer polarity to the cell. Microtubules pull. If the centrosome weren't tied down somewhere, the chromatids and the centrosome would be pulled towards each other, meeting halfway. Realistically, the alignment along the metaphase plate requires shortening and lengthening of microtubules relative to the centriole. The astral microtubules anchor the centrosome so alignment for metaphase and mitosis can occur.

**Kinetochore microtubules** extend from the centrioles of the centrosome and attach to the kinetochore of the chromosomes. Kinetochore microtubules will be changed in length to ensure alignment on the metaphase plate, and will shorten to pull chromatids apart and towards the pole of the cell.

Together, astral microtubules, kinetochore microtubules, and nonkinetochore microtubules (don't worry about this third type—they just connect centrosomes to each other) make up the **mitotic spindle**.

Microtubules are made of dimers of α-**tubulin** and β-**tubulin**. Microtubules have polarity—a **minus end** within the anchor of the centrosome and a **plus end** attached to kinetochores. In anaphase, the microtubules shorten by maintaining contact with the kinetochore on the plus end, and **removing one dimer's-length worth** from the **minus end.** This shortening of the microtubule is associated with a tugging of the microtubule into the centriole, now with the chromatid attached at the kinetochore, toward the cell's pole. Microtubules are discussed in greater detail in General Physiology, Lesson #4.

So imagine now, the plus end of a microtubule attached and unchanging to the kinetochore of a chromatid. The centrosome pulls in the microtubule, reducing its length by one dimer, cleaves the row of dimers away, and repeats. With each "pull," the chromatid gets a little closer to the centriole. And each pull releases a row of tubulin dimers. These tubulin dimers are then used to reassemble the cytoskeleton microtubules from which the spindle microtubules were harvested in the first place.

The details and vocabulary are important only to discuss the process in future lessons, and the disassembly and reassembly are relevant to chemotherapy. Don't spend too much time memorizing the names or types of microtubules; they likely summoned flashbacks to MCAT studying, and that level of biology may be too in-depth for being a doctor.